REMARKS/ARGUMENTS

This Amendment and Response is filed together with a Request for Continued Examination under 37 C.F.R. § 1.114. In the Office Action dated February 25, 2003, all claims are rejected under 35 U.S.C. § 112, second paragraph; 35 U.S.C § 102(b), and/or 35 U.S.C. § 103(a). Applicants respectfully request entry of the foregoing amendments and reconsideration of the rejections in light of the following remarks and arguments.

Status of the Claims

Claims 1, 2 and 24-29 have been amended.

Claims 9 and 11-23 stand withdrawn.

New claims 30-31 have been added.

Claims 1-8 and 24-31 are currently pending.

Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action of February 25, 2003, claims 1-8 and 10 remain rejected, and new claims 24-29 are newly rejected, under 35 U.S.C. § 112, second paragraph, as being indefinite. It is said that there is no definition for the term "acidic buffering potential" or any data which would represent different compositions which produce specific pH's in solution. The claims were examined as though the composition offers at least some hydrogen ions to the surrounding environment (as in the previous Office Action), however. The Examiner states that it is deemed that a composition comprising an acidic calcium phosphate salt may buffer the immediate surroundings of the composition, however Applicants are *claiming* that the composition will buffer any solution, or lower the pH to a specific range in any solution.

Although Applicants believe that the term "acidic buffering potential" is clearly defined in the specification (p. 11, lines 9-19, for example), in the interest of advancing prosecution, and without narrowing the scope of the claims, independent claims 1 and 2 have been amended to omit the objectionable wording. More specifically, the phrase "an acidic buffering potential in physiological solution" has been deleted, and Applicants have amended the claim to read "...wherein said composition, when implanted in a mammal at a site in need of bone growth, is capable of buffering the microenvironment surrounding said site to an acid pH whereby bone growth is enhanced at said site." This wording is supported at p. 11, lines 9-19, and elsewhere in the specification.

With respect to claim 3, Applicants' respectfully traverse this ground of rejection at least for the reason that the particular terms or phrases complained of in claims 1 and 2 are not in claim 3. Claim 3, as previously presented, requires that "wherein the composition, when implanted into a

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mammal, buffers the immediate physiological environment around the composition to a pH between about 4 and about 7."

Claims 24 and 28 have been amended similarly to claims 1 and 2, and now avoid the phrases "the pH of a solution" and "when the bone growth composition is placed in said solution." As suggested by the Examiner, the capability of lowering the pH of the implant's immediate surroundings is now explicitly stated in these claims. Dependent claims 25-27 and 29 have been reworded accordingly to improve their form and clarity.

All of the pending claims, as currently amended, are believed to fully comply with the requirements of 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102(b)

In the Office Action of February 25, 2003 claims 1-5, 8, 10 and 24-27 stand rejected as being anticipated by *Ohura et al.* (1999). The Office Action takes the position that a composition taught by *Ohura et al.* is identical or substantially identical in structure or composition to Applicants' claimed compositions, or are produced by identical or substantially identical processes. It is said that because *Ohura et al.* teach a composition that contains the same ingredients (*i.e.*, monocalcium phosphate monohydrate being one component), that the "buffering potential" must have been an inherent property of that composition.

To anticipate a claim, a single reference must teach every element of the claim -- either expressly or inherently (MPEP 2131.01). The MPEP 2112 also states that, if inherency is asserted, the Examiner must provide rationale or evidence tending to show inherency. More specifically,

> [i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

and

> [t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art)

In the Office Action, the Examiner notes that the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed products (citing *In re Best*, 195 USPQ 430, 433 (CCPA 1977).

Accordingly, Applicants respectfully submit that there is no technical reasoning in the Office Action as to why the specific properties recited in independent claims 1, 2, 3, 24 and 28 would necessarily and inevitably flow from the teachings of the reference. *Ohura et al.* teach a β-tricalcium

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phosphate-monocalcium phosphate monohydrate (β-TCP - MCPM) cement, and also say that the product of that mixture contains β-TCP, MCPM, dicalcium phosphate dihydrate (DCPD), and calcium sulfate dihydrate (CSD). *Ohura et al.* emphasize that the advantage of the β-TCP - MCPM cement is that it is chemically and physically more resorbable *in vivo* than is a corresponding hydroxyapatite cement block. *Ohura et al.* does not teach using MCPM alone as a carrier for BMPs. Given the unpredictability of the art, as noted by the Examiner in the Office Action with respect to the §112, second paragraph rejection, it would not be reasonable to conclude that the combination of β-TCP and MCPM in the cement of *Ohura et al.*, or the resulting mixture of mineral salts in the product, would necessarily possess an acidic character.

As stated in the specification at page 13, lines 5-8, the sparingly soluble calcium phosphate salts act as solution buffers. As the salts increase in calcia concentration (CaO), the pH of a solution increases from about 2 to 11. For example, hydroxyapatite, a widely-used bone growth promoting material, buffers at an alkaline pH. The *Constantz* reference cited by the Examiner also teaches that the pH of solutions of various calcium phosphate salts can vary over a range from acidic to basic (see, for example, col. 4, line 67 - col. 5, line 2; col. 5, line 34-35 of *Constantz*). It cannot, therefore, be assumed that the cement of *Ohura et al.*, or its resulting product mixture, would necessarily cause the implantation site (including the area immediately surrounding the implanted product) to be at an acid pH (claims 1, 2, 4-8), or in the specified acid pH range (claims 3, 24-29) whereby bone growth would be enhanced compared to other bone growth promoting compositions. The pH modulating effects of the other component(s) of *Ohura et al.*'s mixture (*i.e.*, other than monocalcium phosphate monohydrate) must be taken into account. Applicants' specification (at page 13, lines 5-8), suggests that the tricalcium phosphates in solution have an alkaline pH.

The differences between Applicants' claimed compositions and that of *Ohura et al.* are further evidenced by the fact that *Ohura et al.*'s method of making the β-TCP - MCPM cement does not include any provision for ensuring that the product, especially when loaded with an osteogenic protein, would be capable of buffering the microenvironment of the implantation site at an acid pH (claims 1, 2, 4, 5 and 8), and especially not in the specified acid pH ranges of claims 3 and 24-27. Instead, the teaching of *Ohura et al.* appears to be directed toward making a cement composition with favorable porosity characteristics and bioresorbability properties for use as a carrier for BMPs.

The claims, as currently amended, require that the claimed composition, when implanted, be able to buffer or lower the pH of the immediate environment surrounding the implant to an acid pH, or to a pH within a specified acid pH range. Such characteristic or property of the claimed compositions is not expressly or inherently disclosed by *Ohura et al.* As a result, a composition like

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that of any of claims 1-5, 8, 10 or 24-27 could not necessarily and inevitably result from the method of *Ohura et al.*

Rejections Under 35 U.S.C. § 103(a)

Kwan et al.* in view of *Constantz

Claims 1-8 and 10 remain rejected and claims 28-29 are newly rejected under 35 U.S.C. § 103(a) as being unpatentable over *Kwan et al.* in view of *Constantz*. It is said in the Office Action of February 25, 2003 that one of ordinary skill in the art would have expected that the 1:1 ratio of calcium to phosphate added onto a collagen matrix would have been a suitable choice for the production of a bone matrix since *Kwan et al* taught that collagen was a stable support for the calcium phosphate cement, and since *Constantz* taught that brushite and monetite were suitable bone cements. *Constantz* teaches at col. 8, lines 3-12,

> The viscosity of the product may be varied depending on the application. The more basic the product (higher Ca/P ratio) the more the product will be hydroxyapatite, while the more acidic the product, the more the product will approach the properties of brushite. By varying the product crystal structure, percentages of solids, and presence of other additives, the viscosity may be selected to allow for ease of administration to the site to be treated.

In addition to fluidity, or viscosity, other variable properties of the compositions contemplated by *Constantz* appear to include mechanical and physical properties such as porosity, compressive strength, bulk permeability, and surface area.

Product Not the Same. Applicants respectfully traverse the rejection over the combination of *Kwan et al.* and *Constantz* for at least the reason that, even if the teachings of the references were combined as suggested in the Office Action, the resulting product would not be the same as the composition claimed by Applicants because *Kwan et al.* teaches adjusting the pH of the final mineralized collagen slurry to 7.5 ± 0.5 followed by freezing and lyophilization. By adjusting the pH of an ionizable salt solution (such as a brushite or monetite solution), the identity of the predominant resulting crystalline salt species can be altered from that of the original salt. *Kwan et al.* also teaches that the mineralized collagen matrix maintains its physical integrity and porosity for a period of time after implant into a physiological environment in which bone replacement is occurring (col. 4, line 61 - col. 5, line 1 of *Kwan et al.*). Given this teaching by *Kwan et al.*, which is believed to be representative of the conventional thinking at the time of the invention that bone growth is best accomplished at physiological conditions, it would have appeared to one of ordinary skill in the art to be counterintuitive for Applicants' to deliberately devise bone growth compositions that alter the normal physiological environment of an implant in order to enhance bone growth. There is no teaching or suggestion in either reference to try to establish other than a physiological pH

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environment for effecting bone growth, much less to try to ensure that the bone growth composition itself is capable of providing an acidic microenvironment for bone growth.

Unexpected Results. In the Office Action, the Examiner suggests that Applicants may be reciting a new discovery of an old composition, and that (1) the new discovery is unclear because the specification does not clearly teach where any particular ranges of pH can be established by any of the compositions; and (2) an inherent property of an old composition does not materially change the composition. In reply, Applicants would point out that the specification and Figs. 10 and 11 establish that a composition containing a calcium salt, a phosphate, an osteogenic bone protein, and a substrate, such as collagen, at a pH from 4.5 to 6.5 significantly enhanced bone formation as determined histologically and by mineral mass. (Claims 1, 3-4, 10, 24-29). Also, at page 12, lines 14-18, for example, particularly preferred compositions containing acidic calcium phosphate salts (*e.g.*, calcium monophosphate, calcium hydrogen phosphate and calcium pyrophosphate) are mentioned which are capable of acidifying or buffering the implant's local environment in the acid pH range.

The Applicants' discovery that pH plays a strong role in the osteogenic performance of compositions employing bone growth proteins, with "acidic environments providing dramatically superior results" (page 11, lines 6-9) was unexpected by those of skill in the art at the time of the invention . *Constantz* states that the particular mineral will be affected by the pH, and that the pH of the mixture will generally be in the range of about 5-8 (col. 4, l. 67 - col 5, l. 2) or 5-9 (col. 5, l. 34-35), usually in the range of about 6-7.5 (col. 3, l. 13). Notably, there is no teaching or suggestion that the implantable product must be capable of establishing or buffering the pH of the implantation site at one end of that pH range or the other, or anywhere in between. In addition or alternatively, without waiving the foregoing, it appears that *Constantz* may consider that the pH of the composition is merely a result of the calcium/phosphate ratio employed to achieve the desirable physical and mechanical properties disclosed in that reference. In other words, the pH of the composition would be inconsequential or one pH would be as good as another over the stated range, provided that the desired physical and mechanical properties were present. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP 716.01(a); *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987).

It is also submitted that, given the teachings of the prior art, as discussed above with respect to the pH 7.5 ± 0.5 composition of *Kwan et al.*, one of ordinary skill in the art would expect that a composition which significantly lowered the physiological pH environment of the site of new bone growth would cause the quantity and/or quality of bone growth to decline compared to that obtained

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under normal physiological conditions. Applicants' claimed compositions acidify or buffer the *in vivo* site at acid pH and yet do not suffer from the expected decrease in bone growth promoting ability. An absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness. MPEP 716.02(a); *Ex parte Mead Johnson & Co.* 227 USPQ 78 (BPAI 1985).

Teaching Away. Without the teachings provided by Applicants' disclosure, the artisan would have no reason to try to prepare a bone growth composition that would, when implanted at a site where bone growth was desired, create a non-physiological environment for the implant and the growing bone -- much less, to ensure an acidic environment for bone growth. In fact, as evidenced by the teachings of *Kwan et al.*, one of ordinary skill in the art would have expected a bone growth composition to be capable of functioning best *in vivo* at the slightly alkaline physiological pH (about 7.4). It is likely that the artisan would be motivated by the teachings of *Kwan et al.* to adjust the pH of a calcium phosphate-containing composition so as to ensure preservation of physiological conditions during the bone growth process with the idea of optimizing bone growth thereby.

With respect to claims 28 and 29, even if TGF-β and calcium monophosphate were taught by the cited references, one would still not have the composition of claim 28 or 29 for at least the same reasons as discussed above with respect to claims 1 and 2. One would have no basis for assuming that the product of the combined teachings of *Kwan et al.* and *Constantz* for be able to lower the pH of the local environment of the implant to about 5 - 6 8 and thereby enhance bone growth

For at least the foregoing reasons, claims 1-8, 10 and 28-29 are believed to be patentable over the combined teachings of *Kwan et al.* and *Constantz*.

New Claims

New claims 30 and 31 have been added to ensure coverage of specific embodiments to which Applicants are entitled. Claim 30 is supported in the specification at page 11, lines 20-22; page 13, line 15 and 22-23; page 14, line 1, for example. Claim 31 finds support in the specification at page 13, line 21 - page 14, line 4, for example.

Information Disclosure Statement

In the Office Action of February 25, 2003 it was said that the Information Disclosure Statement filed on September 6, 2002 fails to comply with 37 CFR § 1.98(a)(2), which requires a legible copy of each listed U.S. and foreign patent and each publication, or that portion which caused

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it to be listed. Accordingly, a copy of each reference listed on the Information Disclosure Statement (Form PTO-1449) received by the Office on September 6, 2002 will follow this Response.

Conclusion

Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future. The format of this Amendment and Response to Office Action is believed to conform with the Revised Amendment Practice as described in "Changes To Implement Electronic Maintenance of Official Patent Application Records," 68 Fed. Reg. 38611 (June 30, 2003).

All of the pending claims are believed to be free of the prior art, and reconsideration and withdrawal of the rejections are respectfully requested. If a telephone conference would be helpful in advancing prosecution of this matter, the Examiner is invited to telephone the undersigned representative. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,

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